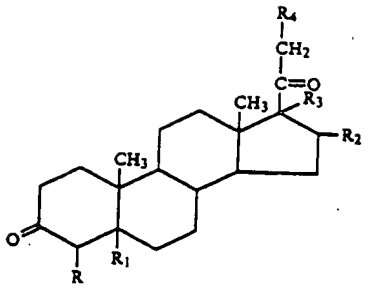

wherein R and R_1 individually are hydrogen or taken together form a double bond; R_2 is hydrogen or methyl; R_3 is hydrogen or hydroxyl; and R_4 is hydrogen or hydroxyl.

16. (New) The method according to claim 8 wherein the progestational agent is cortexolone.

A3 cont

17. (New) The method according to claim 8 wherein the progestational agent is 5-α-pregnan-3,20-dione.

REMARKS

Reconsideration of this application and entry of the foregoing amendments are respectfully requested.

Claims 8 and 10 have been revised to define the invention with additional clarity. New claims 14-17 have been added. The claims as presented are fully supported by

an enabling disclosure (as regards the compound types now recited in claim 10, attention is directed to the paragraph bridging pages 4 and 5 of the application; as regards new claims 14-17, attention is directed to USPs 4,902,681 and 4,908,358, cited on page 4 of the application and incorporated by reference at page 15). That claims have been amended should not be construed as an indication that Applicant agrees with any position taken by the Examiner. Rather, the revisions are made merely to advance prosecution and Applicant reserves the right to pursue any deleted subject matter in a continuation application.

Claims 8-12 stand rejected under 35 USC 112, second paragraph, as allegedly being indefinite. Withdrawal of the rejection is believed to be in order in view of the above-noted claim revisions and for the reasons that follow.

The Examiner objects to the phrase "effect on the function of the sex organs … less than that of medroxyprogesterone". The phrase, as it appears in claim 8 as now presented, reads "effect on the function of the sex organs … less than that of an equivalent dose of medroxyprogesterone" (underlining added). It is submitted that it would be self-evident that when making a comparison such as that referenced in the claim, equivalent doses

would be used. However, for purposes of clarity same is now specifically recited.

As pointed out previously, one skilled in the art would fully appreciate the nature of the functional effects intended. Again, attention is directed to the portions of the Physician's Desk Reference (PDR) (1999) of record relating to medroxyprogesterone acetate (MPA). The PDR portions make clear the effects of MPA on the function of sex organs both from the standpoint of clinical pharmacology and adverse reactions. Applicant has previously provided technical articles that describe the effects of MPA on the function of sex organs of various species of males (including primates). Additional articles describing the effects of MPA on the function of sex organs of females (see Croxatto et al, Contraception 54:79 (1996) and Whitehead et al, Obs. Gyn. 75(4)S:59S (1990)) were also submitted.

Given the PDR portions and representative technical publications provided, it will be evident that the effects of MPA on the ovary and uterus are well established. In the ovary, it prevents follicular maturation and ovulation by inhibiting production of gonadotropins. In the uterus, it induces uterine endothelium to become secretory and vascular, leading to menstrual bleeding irregularities.

The effects of medroxyprogesterone on testicular function are also well established. It results in a reduction in the level testosterone and induces impotence. No indefiniteness results in the use of the present language.

The effects of progestational agents on uterine function can be measured by the affinity of the binding of the progesterones to the rabbit uterus. Terenius (copy previously provided) teaches that 17-hydroxyprogesterone (recited in claim 9) and related progestational agents have a lower affinity for the rabbit uterus than does MPA.

The revision of claim 10 to recite specific compound types is believed to address the Examiner's concerns regarding this claim and claims depending therefrom.

Given the foregoing, it is submitted that the language of the present claims is indeed definite and reconsideration is thus requested.

Claims 8 and 9 stand rejected under 35 USC 103 as allegedly being obvious over Aristoff et al and Blei et al in view of Kuzuya et al. Withdrawal of the rejection is submitted to be in order for the reasons that follow.

The claims relate to a method of reducing atherosclerotic plaque load in the vessels of a patient.

As pointed out by the Examiner, Aristoff et al relates to a method of inhibiting angiogenesis. The method of the

reference involves the administration of a combination of a suramin-type compound and an angiostatic compound, 17 α-hydroxyprogesterone being an example of an angiostatic compound (administration of an angiostatic compound alone is not taught).

As the Examiner acknowledges, Aristoff et al does not teach the use of 17-hydroxyprogesterone to reduce atherosclerotic plaque. In fact, the article says nothing of reducing plaque load but rather refers to the treatment of diseases of neovascularization using the suramin/angiostatic compound combination. Nothing in the citation would have suggested the administration to a patient of the present progestational agents in an amount and under conditions such that plaque load is reduced, as required by the present claims.

While, on its face the Examiner appears to rely on both Blei et al and Kuzuya et al to cure the deficiencies of Aristoff et al, the comments on page 5 of the Action suggest greater emphasis is on the teachings of Kuzuya et al. In any case, these references would in no way have cured the fundamental failings of Aristoff et al for the reasons set forth below.

Turning first to Kuzuya et al, this citation reports the results of *in vitro* - not *in vivo* - studies, such

studies in the context of the present method are of questionable therapeutic relevance. Further, Kuzuya et al makes reference to the "association" between neovascularization and atherosclerotic plaque formation. **It does not demonstrate that neovascularization is causative**. Additionally, Kuzuya et al repeatedly couches the "role" of neovascularization in atherosclerotic plaque formation in terms of it being "possible" (see title) or "postulated" (see abstract). In the abstract, it is stated that "the mechanism and stimulus for neovascularization in atherosclerotic plaque are unknown". On page 665, right column, first paragraph, it is acknowledged that "little is known about pathogenesis of microvessels in atherosclerotic plaque". Thus, by Kuzuya et al's own statements, it is clear that these authors do not view their studies as demonstrating that "angiogenesis is known to be a contributive factor in the progression of atherosclerotic plaque", as the Examiner contends.

It is important to note the very real possibility that the neovascularization "associated" with plaque formation is actually a protective mechanism. That is, new blood vessel formation in the area of a plaque may result from the need for increased blood flow in that area. Nothing is found in Kuzuya et al that is inconsistent with this

possibility and the results of a number of studies published prior to the effective filing date of the present application (discussed below) are very much consistent with this possibility.

Different types of angiogenesis and neovascularization were, in fact, well recognized prior to March of 1999 (the filing date of the provisional application from which this case claims priority). For example, collateral blood vessel formation had been shown to be beneficial in the coronary artery circulation of the heart. Studies by Ramanathan et al (J. Lab. Clin. Med. 125:66 (1995) - copy attached) had demonstrated that developing collaterals augmented coronary blood flow after acute coronary occlusion and these recruitable collaterals significantly reduced infarct size. Pijls et al (J. Am. Coll. Cardiol. 25:1522 (1995) - copy attached) had demonstrated that in 29 of 120 patients undergoing coronary angioplasty, no heart ischemia was present and in these 29 patients fractional collateral blood flow was >24%. During a follow-up period, 16 of the 120 patients studied had an ischemic event, 15 of the 16 were in the group with insufficient ($\leq$23%) collateral flow ($p<0.05$). In addition, Williams et al (Am. J. Cardiol. 37:345 (1976) - copy attached) had demonstrated that well functioning anastomotic channels to the distal

trunk of a blocked coronary artery may afford protection of pump function and improve prognosis in acute myocardial infarction. Further, Hansen (Am Heart J. 117:290 (1989) - copy attached) had demonstrated that "[g]ood collaterals protect the myocardium by prevention of acute myocardial infarction and heart failure and thus improve survival". Habib et al (Circulation 83:739 (1991) - copy attached) had also demonstrated that "the presence of coronary collateral vessels at the onset of myocardial infarction is associated with limitation of infarct size as assessed enzymatically and with improved ventricular function on discharge as assessed by LVEF" (left ventricular ejection fraction). More recently, Billinger et al (J. Am. Coll. Cardiol. 40:1545 (2002) - copy attached) demonstrated the beneficial impact of well developed collateral vessels on the occurrence of future major cardiac ischemic events in a population with chronic stable coronary artery disease undergoing quantitative collateral measurement.

In connection with all of the above, Applicant points out that coronary artery disease and myocardial infarction are caused by atherosclerotic plaque.

The basis for the Examiner's reliance on Blei et al is unclear. However, Applicant points out that plasminogen activators were well known to stimulate fibrinolysis and to

inhibit thrombosis involved in atherosclerosis. Plasminogen activators are used therapeutically in early stages of thrombosis to dissolve clots. Thus, Applicant submits that inhibition of plasminogen activator activity by an angiostatic steriod would be expected to promote thrombosis rather than inhibit thrombosis.

In view of the above, it will be clear that the presently claimed invention would not have been obvious over the combination of teachings upon which the Examiner relies. Reconsideration is requested.

Claims 10-13 stand rejected under 35 USC 103 as allegedly being obvious over Cincotta in view of Gruijter et al. Withdrawal of the rejection is submitted to be in order for the reasons that follow.

As Applicant has pointed out previously, Cincotta relates primarily to a method of reducing restenosis in a mammal undergoing a non-bypass invasive procedure. As indicated in the paragraph bridging columns 1 and 2 of the citation, restinosis results from a complex series of events. The method of inhibiting restenosis comprises administering a dopamine-potentiating/prolactin-reducing compound (halperidol being an example of a prolactin enhancer) to reduce blood prolactin levels during at least

a portion of the daylight hours and continuing that administration during the healing period of the injury.

The Examiner states: "Cincotta et al. does not expressly teach the use of haloperidol specifically in a method of reducing atherosclerotic plaque." The Examiner relies on de Gruijter et al to cure the acknowledged failings of Cincotta. de Gruijter et al, however, is an *in vitro* not an *in vivo* study and thus, as indicated above, of questionable relevance to the claimed therapeutic method. The Examiner offers nothing by way of evidence to support his/her apparent position to the contrary.

Further, de Gruiter et al is based on monocyte binding studies. Monocytes are naturally adherent cells, making such binding studies difficult to interpret.

Of further significance is the fact that the beneficial effects of haloperidol on plaque load described in the present application cannot be ascribed to a reduction in serum triglyceride levels (see Example 1).

In view of the above, reconsideration is requested.

The Examiner is requested to initial and return the PTO 1449 Form(s) submitted herewith.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached

page is captioned "**Version With Markings To Show Changes Made**."

This application is submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

8. (Twice Amended) A method of reducing an atherosclerotic plaque load in the vessels of a patient [mammal] comprising administering to a patient [mammal] in need of such reduction a progestational agent that has an effect on the function of the sex organs of said patient [mammal] less than that of an equivalent dose of medroxyprogesterone acetate, wherein said agent is administered in an amount and under conditions such that [sufficient to effect] said reduction is effected.

10. (Amended) A method of reducing an atherosclerotic plaque load in the vessels of a patient [mammal] comprising administering to a patient [mammal] in need of such reduction a non-steroidal compound that inhibits macrophages or macrophage function, wherein said compound is a benzazepine, a butyrophenone or a benzothiophene and is administered in an amount sufficient to effect said reduction.